Clinical Impact and Significance of Serum Lipoprotein (a) Levels on Cardiovascular Risk in Patients With Coronary Artery Disease

Hiroshi Yoshida, MD, PhD

Lipoprotein (a) [Lp(a)] is composed of apolipoprotein(a) [Apo(a)] bound covalently to the apolipoprotein B of a low-density lipoprotein (LDL)-like particle.1,2 It exerts atherogenicity via its LDL moiety and proinflammatory responses because of accumulated oxidized phospholipids, and it is potentially involved in prothrombotic effects via the plasminogen-like Apo(a) moiety.2-4

Lp(a) is an independent risk factor for cardiovascular disease (CVD).3,4 When the size of Apo(a) is small, the concentration of Lp(a) is high, and there is a high risk of CVD. Single-nucleotide polymorphisms have been revealed in genes that reflect this correlation.4,8 These data have established Lp(a) as a CVD risk factor, but the most of the evidence is based on studies of individuals without previous CVD and without intensive secondary prevention therapies.

By contrast, the role and handling of elevated serum Lp(a) in patients with previous CVD and on lipid-lowering therapies remain less clear because of inconsistent results shown in previously reported papers.8,9 Several studies have shown that increased Lp(a) remains predictive for CVD risk at LDL-cholesterol levels <70 mg/dL,8 but the other studies suggest a positive association only when LDL-cholesterol is ≥130 mg/dL.9 A recently reported meta-analysis of 7 placebo-controlled statin outcome trials (n=26,096) has shown that a relationship of elevated serum Lp(a) levels at 30–50 mg/dL and >50 mg/dL at baseline or on-treatment to an increased hazard ratio of CVD events was evident and pronounced independent of other CVD risk factors despite statin treatment.10 In addition, a combined study of Danish general population studies has shown that elevated serum Lp(a) levels and corresponding LPA risk genotypes for a low number of Apo(a) kringle IV type 2 repeats were causally associated with an increased risk of heart failure partly mediated by myocardial infarction and aortic valve stenosis.11 However, no data are available regarding the relationship between serum Lp(a) levels and clinical outcomes in patients with coronary artery disease (CAD) and systolic dysfunction of the left ventricle (LV).

In this issue of the Journal, Shitara et al12 demonstrate that high levels of serum Lp(a) ≥21.6 mg/dL could be associated with long-term adverse clinical outcomes in patients with CAD and LV systolic dysfunction. They analyzed 369 patients with LV systolic dysfunction defined as LV ejection fraction <50% in a total of 3,508 patients who underwent percutaneous coronary intervention (PCI). The primary outcome (a composite of all-cause death and readmission for acute coronary syndrome and/or heart failure) was assessed in 2 groups according to a median level of Lp(a) (higher Lp(a) group: Lp(a) ≥21.6 mg/dL, n=185; lower Lp(a) group: Lp(a) <21.6 mg/dL, n=184). Eventually, treatment to an increased hazard ratio of CVD events was evident and pronounced independent of other CVD risk factors despite statin treatment.10

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Table. Reference or Optimal Levels and Cutoff Values for Abnormal or High-Risk Levels of Lp(a) Among Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Lp(a) value</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Cardiovascular Society</td>
<td>&gt;30 mg/dL</td>
<td>Risk factor for ASCVD</td>
</tr>
<tr>
<td>European Atherosclerosis Society</td>
<td>≥50 mg/dL</td>
<td>Cutoff for abnormal level</td>
</tr>
<tr>
<td>German and UK apheresis guideline</td>
<td>&gt;60 mg/dL</td>
<td>High-risk for ASCVD</td>
</tr>
<tr>
<td>Japan</td>
<td>≤40 (or 30) mg/dL</td>
<td>A candidate for lipoprotein apheresis if established CVD is present</td>
</tr>
<tr>
<td>USA</td>
<td>&lt;30 mg/dL</td>
<td>Low risk for ASCVD</td>
</tr>
<tr>
<td>WHO/IFCCLM</td>
<td>≥50 mg/dL</td>
<td>Risk-enhancing for ASCVD</td>
</tr>
<tr>
<td>WHO/IFCCLM</td>
<td>&gt;50 mg/dL</td>
<td>High risk for ASCVD</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; IFCCLM, International Federation of Clinical Chemistry and Laboratory Medicine; Lp(a), lipoprotein(a); WHO, World Health Organization.
the present study highlighted that high Lp(a) levels were associated with an increased risk of death and the incidence of heart failure and acute coronary syndrome predisposing to heart failure in patients with CAD and LV systolic dysfunction.

Although the assessment of serum Lp(a) levels may provide prognostic benefits to patients with CAD and LV systolic dysfunction, several issues and limitations remain to be resolved. First is the clinical validity of a cutoff level of serum Lp(a) concentration (≥21.6 mg/dL) to distinguish good and bad prognostic outcomes in patients with CAD and LV systolic dysfunction. A clinical practice guideline recently reported by the American College of Cardiology/American Heart Association Task Force shows that Lp(a) ≥50 mg/dL may be considered a risk-enhancing factor, but that in women this cutoff level should be considered only in the presence of hypercholesterolemia. In addition, a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine also has demonstrated Lp(a) ≥50 mg/dL as a cutoff level for the management of atherosclerotic CVD. Namely, cutoff levels are quite different. The reasons for this difference are that the present study subjects were limited to patients with CAD and LV systolic dysfunction, and there are racial differences in serum Lp(a) concentrations. In fact, reference values and cutoff levels of serum Lp(a) vary among countries (Table). Second is the influence of the timing of collection of blood samples as reported by Shitara et al. Lp(a) levels have been reported as possibly increased in the acute phase of ACS or after PCI. In Shitara et al’s study, all blood sampling was unified to early in the morning after an overnight fast, but some sampling data were collected in the acute phase of CAD. This point may be one of the limitations to interpreting this study’s information in individual clinical settings. Third is the influence of test reagents used to measure serum Lp(a). Currently used reagents recognize the construction of Apo(a) kringle IV type 2 repeats, and consequently measured values of Lp(a) may be influenced by Apo(a) phenotypes. Therefore, the cutoff level (≥21.6 mg/dL) of Lp(a) for clinical prognosis may be informative in patients with CAD and LV systolic dysfunction, but should be carefully considered in each clinical case.

The association of Lp(a) with CVD risk has been markedly revealed, but unlike most classical risk factors (LDL-cholesterol and triglyceride), Lp(a) levels are so far relatively less responsive to diet, environmental variables, or available drugs. However, medications for effectively lowering Lp(a), proprotein convertase subtilisin/kexin type 9 inhibitors and antisense oligonucleotides against Apo(a), have been developed over the decades. Evidence of the relevance of Lp(a) to CVD risk is increasingly expected to contribute to the management of CVD risk.

Disclosure
Professor Hiroshi Yoshida received honoraria from Astellas, Bayer, MSD, and Takeda for speaking activities.

References
11. Kamstrup PR, Nordestgaard BG. Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure in the general population. JACC Heart Fail 2016; 4: 78–87.